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REVIEW ARTICLE

Complex Febrile Seizures: Usual and the Unusual

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Abstract
Febrile seizures account for 2 to 14% of all childhood seizures, and one-third of febrile seizures are complex febrile seizures. Despite this, there is a lack of clinical equipoise in the diagnosis and management of complex febrile seizures and this results in significant practice variability amongst physicians. Although febrile seizures are generally noted to be benign phenomenon, complex febrile seizures carry the risk of subsequent epilepsy. Furthermore, long-term neurodevelopmental sequelae have been observed in some cohorts. The presence of both simple and complex febrile seizures have also been documented in sudden unexpected death in childhood cohorts, and there may be similarities in the underlying pathophysiology to sudden unexpected death in epilepsy. Finally, in some cases the presence of complex febrile seizures may herald the onset of a devastating developmental and epileptic encephalopathy (i.e., Dravet syndrome) or Febrile-Infection Related Epilepsy Syndrome (FIRES). In this narrative review the authors explore the current state of management of complex febrile seizures, their neurological sequelae and morbidity as well as rare epilepsy syndromes and conditions associated with them.

Keywords Febrile Seizure · Morbidity · Status Epilepticus · Hippocampal Sclerosis · Febrile Myoclonus

Introduction

Complex febrile seizures (CFS) are a heterogeneous group of disorders with varied seizure characteristics, possible different etiologies, and thus, variable management and prognostic implications. There are no clear consensus guidelines for its management and this has led to significant practice variability. CFS are a type of FS which are characterized by focal seizure semiology, prolonged duration (≥ 15 min) or occurrence of > 1 seizure within 24 h. Some authors also include prolonged FS aborted with an anti-seizure medication (ASM) before 15 min duration, under CFS. If CFS lasts ≥ 30 min or there are recurrent seizures for ≥ 30 min without full recovery of consciousness in between, then it is classified as febrile status epilepticus (FSE).

FS account for 2 to 14% of all childhood seizures, with peak incidence at 12 to 18 mo of age [1–4]. CFS represent 20–30% of all FS. In a prospective hospital-based study from USA ($n = 428$) [5], 16.1% patients with initial FS had focal FS, 13.8% had multiple FS within 24 h, 9.3% had prolonged FS (> 15 min) and 5.1% had FSE. FSE remains an important etiology of childhood status epilepticus (SE) and accounts for 8 to 32% of SE cases [6].

Investigations

"Routine" blood laboratory investigations are generally not indicated and need to be individualized (i.e., directed toward source of fever).

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Lumbar Puncture (LP)

The incidence of CNS infection is low in children with CFS if the neurological and systemic examination is unremarkable. A systematic review and meta-analysis ($n = 14$ studies) showed the pooled prevalence of bacterial meningitis among children with an apparent CFS was 0.6% [7]. The majority of patients with FSE were also found to have normal CSF results; 96% had ≤ 5 WBCs/mm^3 [3, 8]. However, LP may be indicated in patients with signs/symptoms suggestive of meningitis, abnormal neurological examination, pre-treatment with antibiotics, infants < 12 mo who are incompletely immunized or their immunization status is not known or FSE as first presentation of FS.

Electroencephalogram (EEG)

EEG is not recommended in simple FS; however, most guidelines are either reticent or ambiguous regarding the role and timing of EEG in CFS.

Some studies report that EEG abnormalities may be predictive of future risk of epilepsy [9–12]; frontal paroxysmal or focal EEG abnormalities were noted to be predictive of future risk of epilepsy. In another study, an epileptiform EEG had a poor positive predictive value for the development of epilepsy among neurologically healthy or mildly delayed children with a first CFS [13]. EEG abnormalities have also been found to have limited value in predicting FS recurrence, even in the setting of FSE.

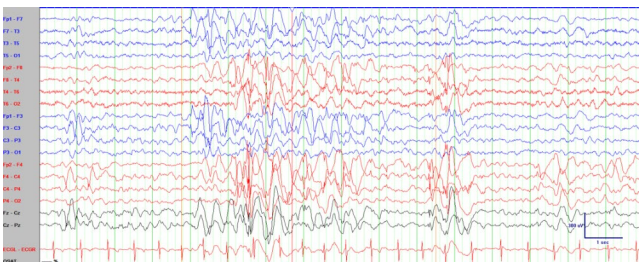

Fig. 1 EEG epoch in a child presenting with apparent complex febrile seizure. A 20-mo-old boy presented with 4 episodes of generalized tonic-clonic seizures (GTCS) (duration 1–1.5 min each) with recovery to baseline in between, within 24 h of fever and cough. Examination was unremarkable besides a mild speech delay. MRI brain was normal. EEG (figure) showed abundant sleep activated epileptiform abnormalities in bilateral hemispheres independently and synchronously. He was discharged on rescue sublingual lorazepam. He continues to have febrile and afebrile GTCS, myoclonic jerks and staring episodes. He was subsequently started on clobazam with partial response; lamotrigine was added later with good clinical response. He is also later diagnosed with autism at 3 y of age. Subsequent genome-wide sequencing showed a de novo hemizygous [mosaic] likely pathogenic variant in *IQSEC2* [c.2588G > C, p.Arg863Pro] gene. (Sensitivity 30 µV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, time-base 30 mm/s, sampling rate 256 Hz; system reference Oz)

Contrasting evidence also exists regarding the yield of EEG in emergent vs. elective setting after CFS. However, the FEBSTAT study showed that 45.2% patients with FSE had abnormal EEGs done within 72 h; focal EEG slowing or attenuation were the most common abnormalities and were highly associated with MRI evidence of acute hippocampal injury [14].

Emergent EEG may be considered in patients with CFS with focal or prolonged seizures, and abnormal neurological examination. This may provide etiological clue, guide the need for emergent neuroimaging and screen for electrographic seizures (e.g. in patients with persisting encephalopathy). EEG may have some role in predicting epilepsy in patients with prolonged FS/FSE. However, it should be noted that many epilepsy syndromes, which may have initial CFS like presentation (i.e., Dravet syndrome), are known to have initial normal EEGs.

A case scenario has been shown in Fig. 1.

Neuroimaging

There are no clear recommendations for neuroimaging in CFS and significant practice variability exists. Neuroimaging may possibly provide a diagnosis and help in prognostication. Further, if it is negative, it can be reassuring to patients' families and physicians. However, there are issues related to radiation, scanning time, incidental findings and cost.

Children with focal and prolonged CFS were more likely to have imaging abnormality as compared to children with SFS in a study of children with first FS [15]; though none of the detected abnormalities warranted urgent medical or surgical intervention [12]. Clinically significant radiological findings requiring urgent intervention in children with CFS have been reported in 1.5–3.8% scanned patients. Frequently, these patients with positive imaging findings had abnormal neurological examination or focal seizure semiology. Data from the FEBSTAT study suggests that prolonged FS may be associated with acute hippocampal signal changes on MRI and this may be predictive of future risk of hippocampal sclerosis (HS) and temporal lobe epilepsy [16–18].

Emergent neuroimaging may be considered in patients with CFS if it is prolonged/FSE or patient has abnormal neurological examination or fails to return to baseline in reasonable time period. In most cases, CT scan should be sufficient. MRI may be preferred in patients with prolonged

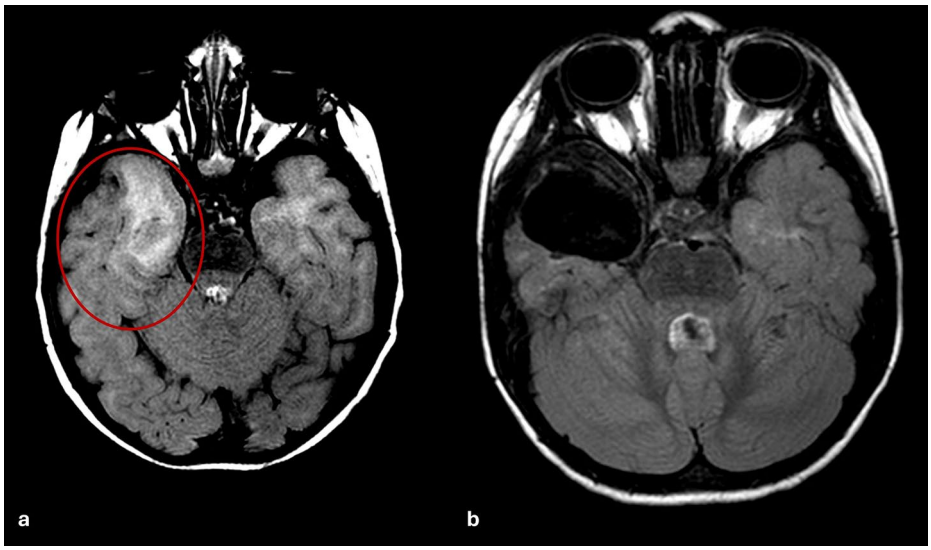

Fig. 2 MRI brain in a child presenting with apparent complex febrile seizure. An 11-mo-old developmentally-normal girl presented with fever, running nose and cough for 1 d. Within 24 h, she experiences an episode of staring, left eye deviation, left arm twitching and drooling x 10 min. She is taken to the emergency room (ER); she is noted to have stable vitals. Another similar episode lasting for 20 min was noted in ER; aborted with intravenous midazolam. She then recovers to baseline after 1 h with normal neurological examination. ER ordered MRI brain [**a**] which showed abnormal T2/FLAIR hyperintensity with mild expansion involving the subcortical and deep white matter of the right parahippocampal and fusiform gyri associated with mild expansion and hazy enhancement of the fusiform gyrus, suggestive of a glioma. Her EEG done next day showed intermittent right temporal slowing. She was discharged on rescue intranasal midazolam. She continued to have afebrile left focal seizures; was subsequently started on oxcarbazepine. She underwent anterior temporal lobectomy at 1.5 y of age [**b**]; pathology showed low grade glioma. She has been seizure free after 2 y follow up

CFS/FSE, significantly abnormal neurological examination or for further characterization of a CT finding.

A representative case has been shown in Fig. 2.

Management

In most circumstances, seizures may have terminated before reaching the hospital. If seizures are ongoing, the institutional status epilepticus protocol should be followed. Once stabilized, detailed history-taking and examination should be undertaken. Antipyretics may be administered, as needed for fever. Anticipatory guidance may focus on overall good prognosis of CFS, risk of future recurrences and epilepsy, home management of seizures, use of rescue medications, and indications for seeking medical attention, which are discussed herein.

Recurrent Febrile Seizures

The risk of recurrence after a first FS is between 30 and 40% and approximately 10% of children will have more than three FS in their lifetime [19]. Risk factors for the development of recurrent febrile seizures include the presence of a family history of FS or epilepsy, age of FS onset lower than 18 mo of age, fever duration < 1 h before seizure onset, lower temperature prior to the initial FS (< 40 ^{0}C) and the presence of complex FS.

Risk of Epilepsy

Risk factors associated with the development of epilepsy after FS include neurodevelopmental abnormalities, complex FS, a family history of epilepsy, age > 3 y at the time of first FS and fever duration < 1 h before seizure onset [20–22]. The risk of epilepsy ranges from 2.4% among children with SFS to 6 to 8% among children with a single complex feature (i.e., focal or prolonged seizures or repeated episodes of FS within the same illness). For children with any two of the complex features, the risk was found to be 17 to 22%, and for those with all three features, 49%.

After FSE the risk of FS is 42.9% and the risk for subsequent FSE is 9.9% [23]. Increased T2 signal on MRI increases the risk of subsequent FSE further. The risk of epilepsy is also increased after FSE and in one study, the cumulative incidence of epilepsy (median follow up 8.9 y) after FSE was 14.3% [24].

Prophylaxis: Anti-Seizure Medications and Antipyretics

The use of antipyretics for the prevention of FS has been the focus of several studies to date, with no evidence to support their use for preventing recurrence. However, they may be administered to help control symptoms related to fever alone.

Home rescue benzodiazepine medication should be prescribed for children with a history of FS lasting longer than five minutes, as these seizures are unlikely to stop on their own. Caregivers should be counselled regarding the benign nature of FS and that the risk of epilepsy and subsequent brain dysfunction is low unless there is a history of prolonged FS.

Routine ASMs are not recommended for children with simple FS. However, intermittent ASM prophylaxis may be considered in certain cases such as in children with frequent CFS, and other considerations such as parental anxiety and access to health care (i.e., live in remote areas). Continuous ASM prophylaxis should be reserved for those with recurrent FSE. Continuous ASM prophylaxis should also be considered for children with neurodevelopmental disorders. There is no consensus guideline regarding the choice of ASM in these settings and age, underlying epilepsy syndrome, co-morbid conditions (i.e., underlying metabolic disorder) should be considered.

A recent Cochrane review demonstrated reduced FS recurrence rates for children that received intermittent diazepam (i.e., at the time of febrile illness) between 6- and 48-mo post seizure and continuous phenobarbital therapy at 6, 12 and 24 mo [25]. However, adverse effects were observed in up to 30% of children who received intermittent diazepam or continuous phenobarbital therapy [25]. Although intermittent clobazam and levetiracetam were shown to have some benefit with reducing the occurrence of FS in the Cochrane review, it was concluded that additional studies are needed to confirm these findings [25]. There was no benefit documented in the review for other therapies (i.e., intermittent phenobarbital, phenytoin, valproate) [25].

Long-Term Outcomes

The long-term outcomes of children with FS have been the subject of several studies over the last decades. Single FS and SFS have not been found to be associated with increased risk of behavioral problems or executive functioning, however more recent studies have shown that children with prolonged or CFS may be at risk of some learning impairments.

Children with CFS have been observed to have lower executive functioning skills when compared to their peers and may be at risk of delayed language and psychiatric disorders. Difficulties with perceptual reasoning and working memory have been documented in children with prolonged, multiple, or focal FS.

Prolonged FS have been associated with difficulties with learning and memory at school age entry as well. Impaired recognition memory was observed one year after prolonged FS in one study [26]. In the FEBSTAT study, outcomes at one year post FSE demonstrated slightly weaker performance on the tasks of receptive language and motor development [27].

Overall, the results from the aforementioned studies suggest that CFS and FSE may be possibly associated with altered neurodevelopmental outcomes. Furthermore, in several studies examining outcomes after FS, neurodevelopmental issues were often identified before the FS onset.

Mortality

Most children with FS have favourable outcomes. For acute FSE, case fatality during hospitalization and 8 y follow up was found to be 0% [28, 29]. While, in a nation-wide population-based cohort study from Denmark, the 30-y cumulative risk of death was 1.9% for children with > 3 FS as compared to 1% in the normal population, albeit the risk was primarily found to be in children who later developed epilepsy [30].

Increased rates of "unexpected" deaths have also been described following FS. In the largest cohort of sudden unexplained death in childhood (SUDC), the prevalence of FS was found to be elevated in SUDC (28.8%) and sudden explained death in childhood (SEDC) (22.1%), when compared to the general population [31]. Furthermore, in a study comparing parallels among SUDC, sudden unexpected death in epilepsy (SUDEP) and sudden infant death (SID), 31.7% of SUDC cases had a history of FS and in 74.4% these were simple FS [32]. Prone position at death, death during sleep and unwitnessed deaths were observed in the SUDC, SID and SUDEP cohorts [32]. It was proposed that in children with SUDC and a history of FS, a terminal fever may increase the risk for an unwitnessed terminal seizure and ultimately death; similar to proposed SUDEP pathophysiology [32].

Unusual Presentations

Unusual Evolution

Genetic Epilepsy with Febrile Seizures Plus (GEFS+)

Genetic epilepsy with febrile seizures plus (GEFS+) is an autosomal dominant familial genetic epilepsy syndrome with variable penetrance and expressivity. The most common phenotypes associated with GEFS+ include FS and

FS+. In FS+, FS may start before the age of six months and continue to occur after the age of six years. In FS + afebrile seizures may occur as well, and these may be limited to the period of FS or occur after the FS cease. Other epilepsy phenotypes associated with GEFS + include myoclonic-atonic epilepsy (MAE), variable genetic generalized epilepsies (GGEs) and focal epilepsies.

GEFS+ is a genetically heterogenous disorder and several different pathogenic variants in epilepsy-related genes have been described and 30% of cases will have a positive result. Most commonly, families will carry a pathogenic variant in the *SCN1A* gene. Additional genes that have been associated with a GEFS + phenotype include *SCN2A*, *SCN1B*, *SCN9A*, *GABRG2*, *GABRA1*, *GABRB3* and *STX1B.*

Dravet Syndrome

DS is a severe developmental and epileptic encephalopathy with onset in the first year of life. In a recent study, median age of onset of seizures was found to be 5.7 mo (range 1.5–20.6 mo) and 98% had seizure onset before one year [33]. The most common seizure types identified in DS were hemi-clonic seizures [35%] and tonic-clonic seizures [52%], and only 55% of seizures were associated with fever [33]. Vaccination was found to trigger seizures in 46% of patients with DS. Approximately 80–90% of patients with DS will have a pathogenic variant in the *SCN1A* gene.

Vaccination Status and DS Pathogenic variants in *SCN1A* may be found in children who present with FS following vaccination. In one study of 144 patients with FS, only three patients (2%) had pathogenic variants in *SCN1A* [34]. Two of the children with pathogenic *SCN1A* variants, had vaccine provoked FS (> GTCs > 15 min) and developed the features of DS. The third child had a FS which was not felt to be related to a vaccine and was diagnosed with GEFS+ [34]. In another study of a Dutch cohort of children that presented with seizures following vaccination, of all seizures that were reported following vaccination in the first year of life, 2.5% were due to DS [35]. The seizures with DS occurred more with a body temperature below 38.5 ^{0}C and reoccurred more often after following vaccinations than those without DS. Furthermore, age of FS ≤ 7 mo, total number of seizures ≥ 5, and prolonged seizures lasting > 10 min were found to be significant risk factors for the development of DS in one study.

Some groups have recommended genetic testing in developmentally normal, 2–15-mo-old children presenting with a single prolonged (5–29 min) hemiclonic seizure or focal/generalized SE (≥ 30 min) of unknown etiology in the context of vaccination or fever but no consensus exists.

Genetic Generalized Epilepsies [GGEs]

A history of FS may be encountered in a number GGEs. A history of FS may be found in 10–15% of children with childhood absence epilepsy and occasionally children with other epilepsy syndrome may have FS as well (i.e., juvenile absence epilepsy, juvenile myoclonic epilepsy, MAE etc.).

Hippocampal Sclerosis

Variable rates of history of FS [10–64%] or prolonged FS/FSE [35–50%] have been reported in pediatric or adult temporal lobe epilepsy cohorts. The FEBSTAT study ($n = 191$) showed that 11.5% children aged < 5 y with FSE showed hippocampal T2 signal changes on MRI done within 72 h [16]; these frequently evolved to hippocampal sclerosis (HS) after 1 y follow-up [17]. Six developed mesial temporal lobe epilepsy after 10-y follow-up; two of them had definite evidence of HS at 1 y follow-up MRI [18].

The possible mechanisms of epileptogenesis after FS are poorly understood and may include increased pro-inflammatory cytokines, endocannabinoid signaling mediated regulation of GABAergic interneurons and glutamatergic neurons, effects on ion channels, genetic predisposition (see GEFS+) and changes in DNA methylation. Further, dysplastic lesions within the mesial temporal structures may predispose to seizures including CFS and could favor the development of HS during the childhood.

Closely Related Phenotypes

Febrile Myoclonus

Febrile myoclonus is an uncommon but distinct form of FS. These occur in previously healthy children aged between 6 mo and 6 y, usually within 24 h of onset of fever. They can occur singly or in clusters of variable duration; rarely, these may culminate in a FS. They usually disappear with the end of fever but may recur with subsequent febrile illness. There may be a family history of FS. EEG and imaging are normal. The neurodevelopmental outcomes are usually benign.

Benign Convulsions with Gastroenteritis (CwG)

In young children, seizures may be seen with acute gastroenteritis even in absence of fever. These have been called benign convulsions with gastroenteritis (CwG) and are characterized by afebrile cluster of focal or generalized seizures, usually brief (< 5 min), within 6 d of viral gastroenteritis in a previously healthy child aged < 6 y (highest incidence in children aged 1–2 y). There may be a family history of epilepsy or febrile seizures in 9.1–17.1% cases.

Table 1 Fever-triggered disorders with seizures and acute encephalopathy

Disorder; affected age groups	Fever	Clinical presentation	Relevant investigation findings	Course
Febrile infection-related epilepsy syndrome (FIRES); Any age (common between 2–17 y)	2 wk to 24 h prior to onset of NORSE	Refractory or super-refractory focal (classically, mesial temporal/opercular localization) and generalized seizures, encephalopathy	MRI may be normal, non-specific or may show B/L mesial temporal, neocortical, basal ganglia, claustral or insular signal changes. EEG usually shows background slowing with generalized, lateralized or multifocal ictal and interictal findings. CSF may show mild pleocytosis usually with normal protein and absent OCB	Chronic phase with DRE and variable neurodevelopmental impairments follow after minimal or no silent period after acute phase
Hemiconvulsion hemiplegia-epilepsy (HHE) syndrome; < 2 y of age	Usually concordant with NORSE	Refractory unilateral motor seizures followed by hemiparesis lasting for at least 24 h	MRI shows hemispheric diffusion restriction (perisylvian and parieto-occipital). EEG shows asymmetric background slowing and lateralized ictal and interictal findings. CSF unremarkable	Progress to drug-resistant focal/hemispheric epilepsy after few years in 75% cases
Acute encephalopathy with biphasic seizures and delayed reduced diffusion (AESD); 1–4 y of age	Usually concordant with seizures	Biphasic seizures: Prolonged CFS or FSE followed by a transient recovery period (2–4 d) and then late seizures and encephalopathy. Common triggers: Human Herpes virus-6 and 7, influenza virus, rotavirus, RSV	MRI brain normal initially; day 3–9 may show extensive subcortical white matter diffusion restriction ("bright tree" appearance). EEG and CSF non-specific	Variable neurodevelopmental impairments, epilepsy
Acute necrotizing encephalopathy (ANE), 9 mo-6 y of age	Hours to days prior to the neurological presentation	Viral prodrome followed by (1–3 d) rapidly progressive encephalopathy and seizures. Common triggers: Human Herpesvirus-6 and -7, influenza virus, H1N1, enterovirus, *Streptococcus pneumoniae.* Genetic predisposition: Mutations in *RANBP2* and *CPT II* genes	MRI shows bilateral multifocal symmetrical gray and white matter lesions especially in thalamus with hemorrhagic foci (Target sign). EEG may show background slowing and multifocal ictal and inter-ictal findings. CSF may show mild pleocytosis. Serum transaminase elevated	30% mortality; survivors have variable neurodevelopmental impairments and epilepsy

CFS Complex febrile seizures; *CSF* Cerebrospinal fluid; *DRE* Drug-resistant epilepsy; *NORSE* New-onset refractory status epilepticus; *OCB* Oligoclonal bands; *RSV* Respiratory syncytial virus

The pathophysiology of CwG remains unclear, both direct CNS invasion and cytokine mediated mechanisms are implicated in seizure generation. It has been associated with viral infections with rotavirus and norovirus and rarely with adenovirus, astrovirus and sapovirus.

Patients with CwG have normal blood laboratory diagnostics. Inter-ictal EEG is usually normal; however, focal ictal EEG onset has been reported. Brain MRI is usually normal; transient signal changes in splenium of corpus callosum have been reported, more commonly in rotavirus-associated CwG.

The acute phase of CwG may require treatment with ASMs. Long-term ASMs are not warranted. Seizure recurrence may occur in 4.7–7.7% cases; recurrences can occur with new episodes of gastroenteritis, as FS or as afebrile seizures. Evolution into epilepsy is rare. Neurodevelopmental prognosis is usually excellent.

Children with gastroenteritis can also have FS (febrile CwG). Children with febrile CwG have been reported to have higher rate of CFS when compared with those with FS without gastroenteritis. Seizures associated with febrile CwG are usually longer and more frequent.

Fever and Inflammation Mediated Refractory Seizures and Encephalopathy

Complex interaction between fever, possible infectious trigger, inflammation and brain immaturity may lead to a spectrum of disorders characterized by CFS-like presentation, encephalopathy and refractory seizures [36, 37]. Most of these disorders may be classified as new-onset refractory status epilepticus (NORSE) [38]. Their relevant clinical features have been summarized in Table 1 [37, 39, 40].

Conclusions

FS are a common occurrence in the pediatric age group and one-third of FS may be CFS. Despite their occurrence, there is equipoise regarding the management of this common condition and a need for standardized clinical guidelines. Although, most CFS are not associated with significant neurological sequalae, altered neurodevelopmental outcomes have been reported as well as the future risk of epilepsy. Furthermore, there is growing evidence that FS may rarely be associated with SUDC and this may share a similar

pathophysiology to SUDEP. Additional prospective studies are needed to follow the long-term neurological outcomes of children with CFS.

Authors' Contributions All authors contributed to the literature review and formulating and approving the final draft of the manuscript. PJ will act as guarantor for this manuscript.

Declarations

Conflict of Interest None.

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